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EXAMINER	
OGUNBIYI, OLUWATOSIN A	
ART UNIT	PAPER NUMBER
1645	

NOTIFICATION DATE	DELIVERY MODE
09/30/2008	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

PATDOCTC@fr.com

Office Action Summary	Application No.	Applicant(s)	
	10/584,020	DELAGRAVE, SIMON	
	Examiner	Art Unit	
	OLUWATOSIN OGUNBIYI	1645	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *26 June 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *18 and 24-30* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *18 and 24-30* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *6/26/08*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

RESPONSE TO AMENDMENT

The amendment filed 6/26/08 has been entered into the record. Claims 1-17 and 19-23 have been cancelled. Claims 18 and 24-30 are pending and are under examination.

The text of Title 35 of the U.S. Code not reiterated herein can be found in the previous office action.

Information Disclosure Statement

The information disclosure statement filed 6/26/08 has been considered and an initialed copy is attached. The information disclosure statement fails to fully comply with the provisions of 37 CFR 1.97, 1.98 and MPEP § 609 because:

Copies of an English translation of the lined through foreign documents or portions thereof are not filed. The information referred to therein in these foreign documents has not been considered as to the merits. Applicant is advised that the date of any re-submission of any item of information contained in this information disclosure statement or the submission of any missing element(s) will be the date of submission for purposes of determining compliance with the requirements based on the time of filing the statement, including all certification requirements for statements under 37 CFR 1.97(e). See MPEP § 609 ¶ C(1).

Specification

The disclosure is objected to because it contains an embedded hyperlink and/or other form of browser-executable code. See p. 8 and 9, for example. Applicant is required to delete the embedded hyperlink and/or other form of browser-executable code. See MPEP § 608.01.

Objection Withdrawn

The objection to claim 18 because the claim is dependent on a non-elected claim is withdrawn in view of the amendment to the claim.

Rejections Withdrawn

The rejection of claim 18 under 35 U.S.C. 102(a) as being anticipated by Junqueira et al (Oncogene, May 8, 2003 22:2772-2781) is withdrawn in view of the amendment to the claim.

Rejections Maintained

The rejection of claim 18 and new claims 24-30 under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement is maintained for reasons made of record (office action mailed 12/27/07) and as set forth below. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims are drawn to a method of detecting the presence of a pathogen or disease in a sample comprising:

a) contacting a polypeptide with said sample, wherein said polypeptide comprises an engineered PDZ domain having at least 50% homology with SEQ ID NO: 2, wherein said engineered PDZ domain binds to a target associated with said pathogen or disease state in said

sample; and

b)detecting binding of said polypeptide to said sample

Applicant's arguments and the response:

Applicant urges that the instant amendment to the claims to recite that the PDZ domain has at least 50% homology to the PDZ domain of SEQ ID NO: 2 overcomes the instant rejection. This is not persuasive.

"…An engineered PDZ domain having at least 50% homology with SEQ ID NO: 2" is being interpreted as "an engineered PDZ domain with at least 50% sequence identity with the amino acid sequence set forth in SEQ ID NO: 2".

The genus of polypeptides comprising an engineered PDZ domain with at least 50% sequence identity with the sequence of SEQ ID NO: 2 is large and comprises structurally variant species dues to the plethora of changes that can be made to the amino acid sequence of SEQ ID NO: 2. These changes include substitutions, deletions or insertions into any 50% (at least) of the amino acid sequence of SEQ ID NO: 2. The claims require that members of said genus of variants have the ability to bind any target associated with a pathogen or disease state in a sample. The specification does not teach which 50%, 60%, 70%, 80% etc of the amino acid sequence of SEQ ID NO: 2 can be changed and still results in a protein that binds a target pathogen or disease state. The specification does not teach which of the PDZ variants are specific for a particular target associated with a pathogen or a disease state. The specification does not identify the common structure of the large genus of PDZ domain variants that enables said variant to retain binding to a target associated with a pathogen or a disease state. There is no disclosed correlation between a common structure of the genus of PDZ domain variants with the

function of binding to a target associated with a pathogen or a disease state. The specification does not teach any engineered PDZ domain having at least 5O% homology with SEQ ID NO: 2 that binds to any target associated with a disease state or associated with a pathogen including BclA of *B. anthracis* (or fragments thereof) or a polypeptide having a C –terminal sequence of EFYA or any targets from *Clostridium botulinum* with a dissociation constant of about 100 nM or lower; or a dissociation constant of about 15 nM or lower.

The written description requirement is separate and distinct from the enablement requirement (See also *Univ. of Rochester v. G.D. Searle & Co.*, 358 F.3d 916, 920-23, 69 USPQ2d 1886, 1890-93 (Fed. Cir. 2004)) and adequate written description requires more than a mere reference to a potential method for producing and assaying engineered PDZ domain variants that binds to any target associated with a disease or pathogen. The purpose of the written description requirement is broader than to merely explain how to 'make and use' [the invention] *Vas-Cath, Inc. v. Mahurkar*, 935 F.2d 1555, 1560, 19 USPQ2d 1111, 1114 (Fed. Cir. 1991) but the written description requires Applicants to have possession of the genus of PDZ domain variants that binds to any target associated with a disease or pathogen. The specification does not provide sufficient description for the large and variant genus of polypeptides comprising PDZ domain variants and associated targets such that one skilled in the art would envision what PDZ domain variant would bind particular targets on pathogens or diseases, thus, Applicant was not in possession of said genus as of the time of filing.

The rejection of claim 18 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention is maintained for reasons made of record in the office action mailed 12/27/07.

Applicant's arguments and the response:

Applicant argues that the specification indicates that the sample being used in the detection method is derived from an organism capable of having a disease, and that the sample would be likely to contain a target indicative of the disease, if the disease were present in the organism. One skilled in the art would understand from this disclosure that a disease can be detected in a sample because the sample is derived from a potentially diseased organism and, thus, potentially contains a detectable target associated with the disease.

Applicant's argument is carefully considered but not persuasive. Disease is defined in the dictionary as a disorder of structure or function in a human, animal or plant, especially one that produces specific symptoms (See compact Oxford English dictionary definition cited previously). Applicant's own arguments states that the disease is present in the organism and that the sample comprises a target indicative of the disease. The instant claims do not reflect that the sample is derived from a potentially diseased organism as indicated by Applicant and in the specification which discloses detection of targets associated with disease in samples obtained from a mammal (p. 22 line 14 to p. 28).

The rejection of claims 18 and new claims 28-30 under 35 U.S.C. 102(e) as being anticipated by Lu et al (US 2004/0018487 A1 Jan. 29, 2004 now US patent 7,312,041 B2 Dec. 25, 2007) is maintained for reasons made of record in the previous action (mailed 12/27/2007) and as set forth below.

The claims are drawn to a method of detecting the presence of a pathogen or disease in a sample comprising:

a) contacting a polypeptide with said sample, wherein said polypeptide comprises an engineered PDZ domain having at least 50% homology with SEQ ID NO: 2, wherein said engineered PDZ domain binds to a target associated with said pathogen or disease state in said sample; and

b)detecting binding of said polypeptide to said sample.

Lu et al teach a method for detecting the presence of an oncogenic human papilloma virus (HPV) protein in a sample comprising contacting a sample suspected of containing oncogenic HPV E6 protein with a polypeptide (SEQ ID NO: 17, see attached sequence alignment) comprising an engineered (i.e. modified by in vitro manipulation, see column 12 PDZ domain variants and see column 18 for production of fusion proteins containing PDZ domains) PDZ domain having 91.1% sequence identity with the amino acid sequence set forth in the instant SEQ ID NO: 2 , wherein said engineered PDZ domain binds to said HPV E6 protein in said sample and detecting binding of said PDZ domain to said HPV E6 polypeptide (columns 295-297 claim 1). Said method is used to detect HPV E6 that may result in oncogenic cellular transformations or biological abnormalities in a variety of cell types (i.e. disease states) and said method is used to detect the presence of HPV that results in diseases such as cervical cancer,

penile cancer, anal cancer and throat cancer (column 4 lines 25 to 35). Thus, Lu et al teaches the presence of a disease state in samples obtained from a subject via detection of HPV E6 proteins. Lu et at teach said polypeptide comprising the PDZ domain further comprises a reporter group such as GST (column 18). Since the polypeptide of Lu et al meets the structural limitation of the instant polypeptide, said polypeptide of Lu et al binds to said HPV E6 with a dissociation constant of about 100 nm or lower absent evidence to the contrary. Said polypeptide of Lu et al binds to said HPV E6 with a dissociation constant of about 15 nm or lower absent evidence to the contrary.

Applicant's arguments and the response:

Applicant argues that Lu et al does not teach a PDZ domain having at least 50% homology with the hCASK PDZ domain. This is not persuasive. To the extent that Applicants are comparing the amino acid sequence of an engineered PDZ domain with the amino acid sequence of SEQ ID NO: 2, then Lu et al teaches a PDZ domain (SEQ ID NO: 17 having 91.1% sequence identity with the amino acid sequence set forth in the instant SEQ ID NO: 2). See attached sequence alignment.

New Rejections Based on Amendment

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to

enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 18 and 24-30 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The claims are drawn to a method of detecting the presence of a pathogen or disease in a sample comprising:

a) contacting a polypeptide with said sample, wherein said polypeptide comprises an engineered PDZ domain having at least 50% homology with SEQ ID NO: 2, wherein said engineered PDZ domain binds to a target associated with said pathogen or disease state in said sample; and

b)detecting binding of said polypeptide to said sample.

The claims require the use of an engineered PDZ domain having at least 50% homology with SEQ ID NO: 2 to bind any target associated with any pathogen or any disease state. The specification refers to an engineered PDZ domain as modified by in vitro manipulation; non-naturally i.e. a PDZ domain whose properties including sequence have been changed by in vitro mutation and having different binding specificity or affinity; and includes an evolved PDZ domain that has been subject to directed evolution or other in vitro evolution techniques (p. 7 lines 26-33. p. 10 lines 13-31). The specification teaches that SEQ ID NO: 2 is the PDZ domain

of hCASK i.e. human CASK protein (p. 7 line 36). The specification contemplates a wide variety targets associated with a large number of disease states or pathogens to be detected including allergies (IgE, IL-5, Il-17), IgA, IgD, IgM or IgG), cytokines, beta 2 macroglobulin, cancers e.g. prostate specific antigen, Alzheimer's (amyloid beta protein), bacterial and viral and fungal proteins etc (see specification p. 11 lines 12-27 to p.13 lines 1-6).

The specification does not provide guidance as to using engineered PDZ domains having at least 50% homology with SEQ ID NO: 2 to detect any pathogens or any diseases (in a sample) via binding of said engineered PDZ domains with any target associated with said pathogen or disease state. The specification does not provide guidance as to engineered PDZ domains having at least 50% homology with SEQ ID NO: 2 and which of these binds to any particular target associated with any disease or any pathogen. The specification does not match up which engineered PDZ domain having at least 50% homology with SEQ ID NO: 2 binds to a particular identified target sequence associated with a pathogen or disease state (see breadth of targets above) and wherein said binding is sufficient for detecting the presence of a pathogen or disease in a sample. The specification discloses PDZ hCASK domain variants that are capable of binding to a peptide from protein BclA of B. anthracis (p. 30 lines 30-35) and the specification teaches an assay to confirm that PDZ hCASK domain variants bind to the full length BclA protein (p. 31 lines 1-14). However, the specification does not teach disclose the sequence homology of these variants (i.e. whether the amino acid sequence is at least 50% homologous to SEQ ID NO: 2) and does not teach the results of whether these variants are able to bind to the BclA protein and does not teach whether binding of these variants to BclA protein or the BclA peptide is sufficient to detect *B. anthracis* in any sample. The specification also provides a

prophetic example of using PDZ domain variants to detect binding to the light chain of botulinum toxin of *Clostridium Botulinum* (example 22). Also, the specification does not teach the sequence homology of any of these PDZ domain variants (i.e. whether the amino acid sequence is at least 50% homologous to SEQ ID NO: 2) or even the sequence structure of these PDZ domain variants and does not teach whether any of the PDZ domain variants binds to the light chain of the botulinum toxin. The specification is devoid of any working example of the instant method of detecting a pathogen or disease in a sample using a polypeptide comprising an engineered PDZ domain having at least 50% homology with SEQ ID NO: 2 that binds to any target associated with any pathogen or any disease state wherein said polypeptide binds to said target with a dissociation constant of about 100 nM or lower; or a dissociation constant of about 15 nM or lower. The dissociation constants are prophetic, the specification does not disclose any actual engineered PDZ domain having at least 50% homology with SEQ ID NO: 2 that binds to any target associated with a pathogen or disease state with a dissociation constant of 15 nM or lower; or 100 nM or lower.

As to where the target is a polypeptide having a C-terminal sequence of EFYA, the instant specification does not teach which targets associated with a pathogen or disease have a C-terminal sequence of EFYA. The art teaches that PDZ hCASK domain binds to the c-terminal EFYA amino acid sequence of synedecans which are cell surface heparan sulfate proteoglycans taught to act as extracellular matrix receptors (Cohen et al. The Journal of Cell Biology 142: 129-138, 1998, cited in IDS). Without the disclosure of targets associated with pathogens or disease states wherein said target is a protein that comprises the amino acid sequence EFYA and which engineered PDZ domain having at least 50% homology with SEQ ID NO: 2 binds to such

a target (polypeptide associated with pathogen or disease state that comprises EFYA) one of skill in the art cannot use the invention as claimed i.e. to detect the presence of a pathogen or disease in a sample. The specification does not disclose proteins comprising engineered PDZ domains having at least 50% homology with SEQ ID NO: 2, does not disclose the target specificity of said engineered PDZ domains and for which targets associated with disease states and pathogens they bind to, thus the specification as of the time of filing has not enabled one skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention i.e. to detect any pathogen or any disease in any sample, as claimed.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 18 and 24-30 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The claims are drawn to a method of detecting the presence of a pathogen or disease in a sample

comprising:

a) contacting a polypeptide with said sample, wherein said polypeptide comprises

an engineered PDZ domain having at least 50% homology with SEQ ID NO: 2, wherein said

engineered PDZ domain binds to a target associated with said pathogen or disease state in said sample; and

b)detecting binding of said polypeptide to said sample.

Step 'b' i.e. detecting binding of said polypeptide to said sample lacks antecedent basis in the claim because the claim recites that the "engineered PDZ domain binds to a target associated with said pathogen or disease state in said sample". It is not clear what is binding to what. Is the polypeptide binding to the sample or is the polypeptide comprising the PDZ domain binding to a target *in* the sample?

Further, the recitation of " an engineered PDZ domain having at least 50% homology with SEQ ID NO: 2" is vague and indefinite. To the extent that Applicants are comparing the amino acid sequence of an engineered PDZ domain with the amino acid sequence of SEQ ID NO: 2, then percent identity with the amino acid sequence set forth in SEQ ID NO: 2 instead of percent homology is more appropriate. The specification on p. 9-10 teaches that homology can be ascertained using the BLAST 2 sequences program to align two sequences. However, the BLAST 2 sequences program does not give sequence homology but determines sequence similarity or identity of two sequences that are already known to be homologous (Tatusova et al FEMS Microbiol Lett 174: 247-250, 1999). Furthermore, sequence similarity or identity is observable while homology is a hypothesis based on observation (see attached definition of sequence homology http://www.biology-online.org/dictionary/Sequence_homology). Also, see Applicant's reference to at least about 50% identity in p. 8 lines —4)

Status of Claims

Claims 18 and 24-30 are rejected. No claims allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Oluwatosin Ogunbiyi whose telephone number is 571-272-9939. The examiner can generally be reached on M-F 8:30 am - 5:00 pm. If attempts to reach the examiner by telephone are unsuccessful, either of the examiner's supervisors Shanon Foley (571-272-0898) or Robert Mondesi (571-272-0956) can be contacted.

The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

/Oluwatosin Ogunbiyi/

Examiner, Art Unit 1645

/Patricia A. Duffy/

Primary Examiner, Art Unit 1645